Paper for Ion Channels

focus on pp 205-219

On the stochastic properties of single ion channels

BY D. COQQUIST and A. G. HAWKES

† Department of Pharmacoxy, University College London, London WC1E 6BT, U.K.
‡ Department of Statistics, University College of Swansea, Swansea SA2 8PP, U.K.

Communicated by Sir Bernard Katz, F.R.S. – Received 17 April 1980

It is desirable to be able to predict, from a specified mechanism, the appearance of currents that flow through single ion channels (a) to enable interpretation of experiments in which single channel currents are observed, and (b) to allow physical meaning to be attached to the results observed in kinetic (open and relaxed) experiments in which the aggregate of many single channel currents is observed.

With this object, distributions (and their means) are derived for the length of the segments in any specified subset of states (e.g. all closed states). In general these are found to depend not only on the details of the single channel process, but also on aggregate properties, such as the overall occupancy of the channel, and the length of the bursts of openings, that may occur during a single occupancy, and (b) the apparent gap between such bursts. The methods are illustrated by their application to two simple theories of action, that of the "half-basal" or "nonequilibrium" mechanism proposed by Katz. This theory involves a probability of opening at each step, but the number of openings per occupancy, and the apparent burst length, are independent of the condition of the protein, which is a simple cooperative mechanism predicts that both will increase with the amount of the protein.

Introduction

Since the introduction of the mechanism of Katz (1957, 1973), the rate of exchange of drug has become widely used. It is helpful, in the transformation of such experiments, to some physical interpretation can be placed on the rates and amplitudes of the kinetic components that are observed. The basis for such interpretations lies in being able to imagine how (individual ion channel) boxes, and how the currents through individual channels and the probabilities of action can be produced by the channel opening.

The incentive to understand this behavior has become even greater since Naber & Jaklech's (1978) success in observing directly the current through individual channels. It seems that channel openings may be grouped into bursts, e.g. in the presence of channel blocking drugs (Naber & Jaklech, 1978), as had been assumed, or in turn, indirectly from noise and relaxation measurements (for example: Wolff, 1977).
The behavior of ion channels has been characterized in a number of studies in terms of a Markov chain in continuous time. In particular, they derived the distribution of the time spent in a specific subset of states, the open states, denoted O. This result is obtained from the conditional distributions of the lifetimes of the open state, the distribution conditioned on which particular open state the lifetime started in. It is obvious that these results hold for any arbitrary set of states, not only for open states. However, the distribution of the time spent in a specified subset of states depends, in general, not only on the starting state but also on the state that is reached after the specified subset in left. More, more general, conditional distributions are needed, and we derived as follows.

Suppose that the system, as in 1, is completely distinguishable states, and has a matrix of transition rules (assumed not to depend on time) identified \( Q \), as in Coulthram and Hawkes (1977). Consider a subset, \( O \), that contains some of the \( n \) states, and denote the subset of the remaining \( n - |O| \) states. (The states not containing \( O \) can be, for example, be open states, or unopened but shut states. The matrix \( Q \) can be partitioned thus:

\[
Q = \begin{pmatrix} O & \Omega \end{pmatrix}
\]

We define a \( k \times k \) matrix, \( P \), with elements

\[
P_{ij} = \mathbb{P}[\text{state } i \text{ at time } t | \text{state } j \text{ at time } 0] \tag{1.2}
\]

where \( \mathbb{P} \) stands for probability. It is then a standard result (see, for example, Coulthram and Hawkes 1977, eq. (1.9) that

\[
d\mathbb{P}(x)dy = \mathbb{P}(x, y) \tag{1.3}
\]

To find the distribution of the lifetime in \( O \), consider a modified process in which

\[
\mathbb{P}(x, y) = \mathbb{P}(x, y) \tag{1.3.2}
\]
Stochastic properties of ion channels

By J. D. Cockburn and A. G. Hawkes

(his would be only if e were a p.d.d.). Also note, from (1.2) and (1.13), that,

\[ p_{ij}(t) = F(t) \text{ if } i \neq j \text{ and } t \geq e_{ij}(c) \text{ in } i. \]

(1.16)

Therefore

\[ p_{ij}(t) = \sum_{l=0}^{\infty} p_{ij}^{(l)}(t) \text{ for } t \geq e_{ij}(c) \text{ in } i, \quad i, \neq j, \text{ c.d.f.} \]

(1.17)

which is the required probability. Thus, from (1.10) and (1.11), the required conditional p.d.d.s are

\[ f_{ij}(t) = \frac{p_{ij}(t)}{1 - P_{ij}(t)}, \quad i, \neq j, \text{ c.d.f.} \]

(1.18)

Note that, from (1.14), \( p_{ij}^{(l)}(t) \) are the elements of \( Q_{ij}^{(l)} = -Q_{ij}^{T}Q_{ij} \). The Laplace transforms of these are

\[ F_{ij}(s) = -s Q_{ij} f_{ij}(t), \quad i, \neq j, \text{ c.d.f.} \]

(1.19)

which can be obtained from (1.14).

An alternative method, more suitable for automatic numerical computation, is to calculate, as in Cullochon & Hawkes (1977), pp. 234, 241, the matrix \( \Phi_{ij} (b = \ldots, 0) \) of the exponential of \( Q_{ij} \). This is

\[ \Phi_{ij}(b) = \sum_{l=0}^{\infty} e^{-l b} Q_{ij}^{l}, \]

(1.20)

where the \( b \) is the eigenvalues, which is in number (counted distinct) of \( Q_{ij} \). In later sections we shall prove, as in Cullochon (1981) to see the minor eigenvalues, \( \Phi_{ij} (b = \ldots, 0) \) which are positive and constants. This allows calculation of

\[ p_{ij}(t) = \sum_{b=0}^{\infty} \Phi_{ij}^{(b)}(s) / b^{(b+1)} \]

(1.21)

which can be inserted into (1.12) to obtain \( \phi_{ij}(t) \) from (1.13).

The mean of the conditional distribution \( (1.19) \) can be found either as

\[ m_{ij} = -\int_{0}^{\infty} -t f_{ij}(t) dt \]

(1.22)

or, via (1.19), as

\[ m_{ij} = \int_{0}^{\infty} e^{-t} p_{ij}(t) dt \]

(1.23)

Conditions: conditional only at the starting state

If the probabilities in (1.2) are summed over all well states, \( j \) (before \( j = 0 \)), we get the deterministic functions for the lifetime in \( i \), given that this starts in state \( i \). The corresponding p.d.d.s are therefore the \( i \) th elements \( f_{ij}(t) \) of the \( i \times i \) vector

\[ f_{ij}(t) = Q_{ij}^{(i)} f_{ij}(t) = \int_{0}^{\infty} \]

(1.24)

where \( u_{i} \) denotes a \( i \times i \) unit vector. This is equivalent to the result given by

Cullochon & Hawkes (1977, eqs (66)-(68)). It follows from (1.14), and the fact that the row sums of \( Q_{ij} \) are zero, that \( f_{ij}(t) = Q_{ij}^{(i)} f_{ij}(t) = u_{i} f_{ij}(t) \), as expected, from (1.14), for p.d.d.s.

The unconditional distribution of life in \( i \)

This follows from the fact that

\[ P(\text{life in } i \in 0 | \text{ starts in } i) = \frac{P(\text{life in } i \in 0 | \text{ starts in } j) \sum_{j} P(\text{starts in } j) = 1}{1} \]

(1.25)

where

\[ \sum_{j} P(\text{starts in } j) = 1 \]

(1.26)

The \( i \) x \( i \) row vector of \( P(\text{start in } i) = k_{i} \), denoted \( i \), is

\[ \Phi_{ij}(s) = e^{-s Q_{ij}} f_{ij}(t) \]

(1.27)

where the \( i \) x \( i \) row vector \( f_{ij}(t) \) contains the equilibrium overstates of the states in \( i \). Therefore the p.d.d. at the time the p.d.d. is

\[ f_{ij}^{(i)}(t) \]

(1.28)

This is equivalent to the result given by Cullochon & Hawkes (1977, eq. 66); rather than a use is here to avoid confusion of the overstates. They also give (eq. (70)), a simple expression for the mean of \( f_{ij}(t) \).

We only, for the sake of completeness, note that the probability that a population in \( i \) visits a state \( j \), regardless of how the population started, may be found by noting that

\[ P(\text{visits from } i \in 0 \text{ to state } j \in 0 | \text{ starts in } j) = \frac{P(\text{visits from } i \in 0 \text{ to state } j \in 0)}{P(\text{starts in } j)} \]

(1.29)

The best relation follows by direct analogy with (1.27).

The \( i \) th row vector of \( \Phi_{ij}^{(i)} \) contains only one state

Here, \( i \) = state \( i \) (say), and \( \Phi_{ij}^{(i)} = \Phi_{ij} \). Therefore \( Q_{ij}^{(i)} = 0 \). Hence, from (1.14), the \( p_{ij}^{(l)}(t) \) are the elements of \( Q_{ij}^{(i)} = -Q_{ij}^{(i)T}Q_{ij}^{(i)} \), i.e.,

\[ p_{ij}^{(l)}(t) = e^{-t Q_{ij}^{(i)}} \quad j = 0, 1, \ldots, \]

(1.30)

and so

\[ p_{ij}^{(l)}(t) = \frac{1}{t} \int_{0}^{t} e^{-\tau Q_{ij}^{(i)}} d\tau \]

(1.31)

Hence, from (1.10), the Laplace transforms of the p.d.f. of the lifetime in \( i \), given that when the states leave \( i \) of the p.d.d. at state \( i \), is

\[ f_{ij}^{(i)}(s) = \Phi_{ij}^{(i)} f_{ij}^{(i)}(t) = e^{-s Q_{ij}^{(i)}} \]

(1.32)

Inversion gives the p.d.d. as

\[ f_{ij}^{(i)}(t) = \int_{0}^{\infty} e^{-t e^{-t Q_{ij}^{(i)}}} \]

(1.33)

i.e., the time spent in \( i \) (state \( i )) is exponentially distributed, with mean \( -1/e^{Q_{ij}^{(i)}} \), regardless if state \( i = 0 \) follows the state \( 1 \), \( 2, \ldots, \) follows the \( i \) state. This result is exact, and
Stochastic properties of ion channels

where

\[ V(t) = V(t) - \alpha \delta \chi_m \]  

(1.38)

Usually, \( a = 1 \), and so

\[ F(t) = (1 - \alpha \delta \chi_m) \]  

(1.39)

and \( \delta \) is a polynomial of degree \( n < 1 \). Thus, from (1.32), the inverse of \( V(t)/e^{\alpha \delta \chi_m} \) is

\[ \sum_{j=0}^{n} \frac{\alpha^j}{j!} \chi_m^{j-1} \]  

(1.40)

Here, from (1.38), \( F(t) \) has the form of a product of \( n + 1 \) terms \( (\alpha \delta \chi_m) \), for all \( j \neq 0 \).

Some practical problems

Many of the interesting characteristics of the behavior of single ion channels depend on the tendency of openings to be grouped in clusters, or bursts. In the analysis of actual observations, two main attributes must be considered: (a) where the observed opening times, even (or inclusive parts) of the record, all originate from the same ion channel, and (b) where, in common practice, more than one channel may contribute to the observed record, so that it is not possible to be sure that successive openings originate from the same channel. These will be considered separately.

(a) One channel only contributes to the observed record

Long records that all originate from the same channel can be obtained only under rather special circumstances in practice. Salomon et al. (1968) have shown that at high agonist concentrations, which produce openings at high frequency, the record is interpreted with long silent periods as a result of desensitization. It appears (e.g., from the absence of double-sized openings) that the closely spaced openings, seen between these long gaps, all originate from the same channel. In this case there is no a priori reason to be suspicious when opening into clusters, or bursts, of that matter in the (transmembrane) distribution of the time spent in each of the experimentally distinguishable (i.e., open and shut) states.

Nevertheless, if clustering appears "obvious" it may be tempting, and it certainly may be intuitively enlightening, to uncover the characteristics of bursts of openings. For example, it is shown later that the Cattlgs-Blake (non-cooperative) model predicts that the mean burst length should be independent of agonist concentration, whereas a cooperative model predicts that it should increase with agonist concentration. However, in the first model, it would happen that as agonist concentration was increased, that two or more bursts were seen enough that they were increasingly often mistaken for a single long burst. Then the length of the burst would appear, correctly, to increase with agonist concentration. One way to deal with this problem would be to use only low agonist concentrations, as described under (b),

(b) More than one channel contribute to the observed record

In this case, the situation is much more complex. The number of channels contributing to the record is not known, and it is not possible to know from the record how many channels are open at any given time. This makes it difficult to interpret the record in terms of the properties of individual channels. However, under certain conditions, it is possible to make some qualitative observations about the properties of the individual channels contributing to the record. For example, it is possible to determine the mean burst length as a function of agonist concentration, and to compare this with the predictions of the Cattlgs-Blake (non-cooperative) and cooperative models. If the burst length is found to increase with agonist concentration, it is likely that the cooperative model is correct. If the burst length remains constant or decreases with agonist concentration, it is likely that the non-cooperative model is correct.

In conclusion, it is possible to make some qualitative observations about the properties of the individual channels contributing to the record under certain conditions. However, it is not possible to make quantitative observations about the properties of individual channels without knowing the number of channels contributing to the record.

Further references


below. Another way would be to abandon the attempt to distinguish chiropters and to use the unconditional distributions as described above.

A third possibility is to define observed births unambiguously, as any series of openings that is separated from other openings by shot periods longer than some specified value. It is then possible to predict, from the postulated mechanism, the characteristics of the observed births defined in this way. This can be done by the methods of Hawkes [1965], although the theory is straightforward in that it is not applicable to the problem at hand. The results are in good agreement with those given here, and would be better suited with a separate paper.

(b) More than one channel contributes to the observed record

This is usual under most circumstances except those discussed above. If the intervals between openings, for a single channel, have a simple exponential distribution with mean $\mu$, then $\hat{\mu}$ interval $\approx 3\mu^{-1}$. The interval between two openings will be 1 or more, when $n$ channels are responding, only if all of the $n$ individual channels have an interval of 1 or more before next opening. [If the channel behaves independently the above probabilities can be multiplied and the distribution of the observed interval will then be exponential with mean $\mu/n$.] However, if the distributions of the intervals between openings, for a single channel, is not simply exponential (as in the examples below), no such simple result can be obtained. In any case, the value of $\mu$ would not actually be known. As a result, it is not possible to interpret independently the shot periods between openings. However under some conditions it may be possible for openings to be unambiguously grouped into bursts; for example, when the average concentration is sufficiently low, or when the shot periods within bursts are very short. This is shown clearly by the numerical examples given later. In rare cases all the openings within each burst will almost certainly originate from the same channel. Therefore useful information can be inferred from the distributions (2) of the number of openings per burst, (2) of open lifetimes and (3) of shot periods within a burst, even though the distribution of shot periods between bursts will be uninterpretable.

Non-cooperative agonistic action

The simplest plausible mechanism for agonistic action is that suggested by Castello & Rose [1972], namely

\[
T_{\text{trf}} + \Gamma \rightarrow \text{AR} + \Gamma, \\
\text{state: 3} \\
\lambda = \frac{\beta}{2} + \frac{1}{2

The shot combination of the m-polarized channel complex is denoted T, the open combination is denoted R, and $\Gamma$ represents the agonist (concentration $= x_2$, say). The rate constants for agonist binding are $k_1$ and $k_{10}$, and so the limiting equilibrium constant is $K = k_1 \lambda$.

Equilibrium expressions

At equilibrium we have

\[
p_2(\omega) = \frac{p_1(\omega)}{1 + \beta_1 z(\omega), p_3(\omega) = p_2(\omega), p_4(\omega) = \beta_2 p_2(\omega)} \\
\text{where} \ \lambda = \frac{1}{k_1}, \ \beta_1 = \text{the normalized agonist concentration.}
\]

\[
\text{Depiction of bursts and gaps}
\]

The terminology used in this section is defined in figure 1. A burst is defined as a series of emissions in one channel (AT, AB), but some bursts may consist of an opening with no opening, and even when there is an opening the burst, defined by the single channel current, will be shorter than the actual burst (see figure 1).

The number of openings per burst

This has already been given by Colquhoun & Hawkes [1976], in their present notation (12, 33), with the numbering in (2.1) the probability of observing $y$ openings per burst is

\[
P(y) = \frac{\mu^y}{y!} e^{-\mu}, \quad \lambda = 1, 2, \ldots, \infty
\]

where $\rho = \beta(2/k_1 + 1) = x_2$. This is a geometric distribution with mean

\[
\tau = \frac{x_2}{\beta(2/k_1 + 1)} = x_2
\]

\[
\text{It depends only on the relative probabilities that AT will open, or will dissociate. It is (almost) in the competitive case discussed below) independent of the agonist concentration.}
\]
An aggregate host is defined by the presence of at least one opening. The probability of openings per occurrence, given that at least one opening occurs, is

\[ P(d) = \frac{1}{1 - \beta}, \quad d > 0. \]  

(2.5)

with mean

\[ \mu = 1/\beta = 1 + P(d). \]  

(2.6)

**Distribution of the burst length**

The number of states in (2.1) will be used. The expected state in which to remain interested is \((N, H, A)_t\), i.e. (2.1). This will be defined as state 0. Therefore state \(0 = (0, 0, 0)_t\) is the initial state of the remaining states, 3, i.e. \(I\). The conditional Q defined in (1.1) is therefore

\[
Q = \begin{bmatrix}
0 & 0 & \beta \vee 0 \\
\beta & 0 & 0 \\
\beta & 0 & 0 \\
0 & \beta & 0
\end{bmatrix}
\]  

(2.7)

From (1.14) and (2.1),

\[
Q \Delta(t) = \begin{bmatrix}
0 & 0 & \beta \vee 0 \\
\beta & 0 & 0 \\
\beta & 0 & 0 \\
0 & \beta & 0
\end{bmatrix} \begin{bmatrix}
\chi_0(t) \\
\chi_1(t) \\
\chi_2(t) \\
\chi_3(t)
\end{bmatrix}
= \begin{bmatrix}
\beta \chi_0(t) \\
\beta \chi_1(t) \\
\beta \chi_2(t) \\
\beta \chi_3(t)
\end{bmatrix}
\]  

(2.8)

where \(\chi_0, \chi_1, \chi_2, \chi_3\) are solutions of the quadratic \(\lambda^2 - \lambda + \beta = 0\), i.e.

\[
\lambda = \frac{1}{2}(1 - \sqrt{\beta}), \quad \lambda = \frac{1}{2}(1 + \sqrt{\beta}).
\]  

(2.9)

where

\[
\phi = \lambda_0 + \lambda_1 = \lambda_0 + \lambda_2 = \lambda_0 + \lambda_3 = \lambda_0 + \lambda_1 + \lambda_2 + \lambda_3.
\]  

(2.10)

Hence

\[
Q \Delta(t) = \sum_{j=0}^{3} \left( \begin{array}{c}
\lambda_0 \\
\lambda_1 \\
\lambda_2 \\
\lambda_3
\end{array} \right)
\]  

(2.11)

as expected from (1.12), since state 0 must be reached when \(N\) is left (regardless of which state the subject is left in). Thus, from (1.11), (2.8) and (2.12), the Laplace transform of the conditional distribution of the life of \(N\), given that it starts in \(A\) (state 2) and exits to \(T\) state \(I_0\), is

\[
\mathcal{L}(N) = \frac{1}{\lambda_0 + \lambda_1 + \lambda_2 + \lambda_3}
\]  

(2.13)

and given that the life \(N\) is in state 3 (state 2) and exits to \(T\) we obtain

\[
\mathcal{L}(N) = \frac{1}{\lambda_0 + \lambda_1 + \lambda_2 + \lambda_3}
\]  

(2.14)

Inversion of these, with the help of (1.49) gives the actual conditional p.d.f. as

\[
f_d(t) = \frac{\lambda_0 + \lambda_1 + \lambda_2 + \lambda_3}{\beta + \lambda_0 + \lambda_1 + \lambda_2 + \lambda_3}
\]  

(2.15)

**Stochastic properties of ion channels**

The function \(f_{d}(t) = 1/\beta + e^{-t/\beta} - 1/\beta\) is a simple model of the distribution function of the lifetimes of the burst. In (1.22) we find

\[
\Phi = \frac{1}{\beta}
\]  

(2.16)

so, from (1.23), the unconditional distribution of the time spent in \(A\), i.e. the lifetimes of the burst, is

\[
f_{d}(t) = \Phi f_{d}(t) - \Phi f_{d}(t) = \Phi f_{d}(t)
\]  

(2.17)

with mean \(\phi \mu \) given below. This is to be expected because all actual bursts must start in state \(2(\Lambda)\).

From (1.22) or (2.12), the mean time is \(\phi \mu\), given that the play is in \(A\) at the start of state 0, or in state 1, or in state 2, follow, respectively, from (2.7), (2.8), and

\[
\mu = \left( \frac{1}{2}(1 + \sqrt{\beta}) \right) + \left( \frac{1}{2}(1 + \sqrt{\beta}) \right) = \left( \frac{1}{2}(1 + \sqrt{\beta}) \right) + \left( \frac{1}{2}(1 + \sqrt{\beta}) \right)
\]  

(2.18)

The latter is shorter than the former because a time equal to the mean life of the open state, \(\mu = 1/\beta\). The overall mean is, however, twice this value and can be found more quickly directly from Eq. (74) of Colquhoun & Hounslow (1977). If \(\phi\) is interchanged with \(\Phi\) and of \(\phi\) in that equation. All of the mean lifetimes are independent of agonist concentration (unlike the cooperative case, below).

**Distribution of the number of bursts**

First note (see figure 1) that the time spent in \(A(\Lambda, I, A)\), gives that the life starts in \(A\) and exits to \(\Lambda\) (which sees a p.d.f. given by \(f_{d}(t)\)), consists of the time spent in the burst, plus the time spent in one region in \(A\). The last of these has an exponential distribution with mean \(\mu = (\beta + \lambda_1 + \lambda_2 + \lambda_3)/\lambda_0\), regardless of which state follows it, from (1.32), i.e. the Laplace transform of the p.d.f. is

\[
f_{d}(t) = e^{-t/\beta} - 1/\beta.
\]  

(2.19)

Thus, from (1.30),

\[
f_{d}(t) = \mathcal{L}(\phi f_{d}(t)),
\]  

(2.20)

where \(\phi f_{d}(t)\) is the transform of the p.d.f. of the length of the apparent burst. Thus, from (1.30) and (2.12),

\[
f_{d}(t) = \mathcal{L}(\phi f_{d}(t)),
\]  

(2.21)

Inversion of this, by means of (1.49), gives the p.d.f. as

\[
f_{d}(t) = \frac{\lambda_0 + \lambda_1 + \lambda_2 + \lambda_3}{\beta + \lambda_0 + \lambda_1 + \lambda_2 + \lambda_3}
\]  

(2.22)
This is a sum of the same two approximants as occur in the p.d.f. of the actual burst, but with different coefficients. The mean length of the apparent burst is therefore

\[ m_{ap} = \frac{1}{2} \frac{1}{\lambda_j} \mu_j \left( 1 - \frac{1}{\lambda_j} \right). \]

(2.23)

This is shorter than \( m \) by an amount equal to the mean life in \( AT \). Again it is independent of the apparent concentration.

**Mean open and shut time per burst**

The mean length \( m_{ap} \) of an opening is \( m_{op} = 1/\lambda_j \), and the mean length of a square in \( AT \) is \( m_{sq} = 1/(2\lambda_j) \). The mean open time per burst should therefore be

\[ \mu_{ap} = \frac{\mu_j}{2\lambda_j}. \]

(2.24)

The total open and shut times agree with the mean burst length, \( m_{ap} \) from (2.19).

The mean number of openings per burst, \( \lambda_{op} = \lambda_j \mu_j / \lambda_j \), was derived in (2.6).

The mean open time per apparent burst is therefore

\[ \mu_{ap} = m_{ap} \lambda_j. \]

(2.25)

The mean number of squares in \( AT \) per apparent burst, from figure 1, must be

\[ \mu_{sq} = 1 - \frac{\mu_j}{2\lambda_j} \]

and so the mean shut time per apparent burst will be

\[ \mu_{sh} = \frac{\mu_j}{2\lambda_j} \lambda_j = \frac{m_{ap} \lambda_j}{2}. \]

(2.26)

The total of (2.24) and (2.25) agrees with the mean apparent burst length found in (2.22).

Unlike the cooperative case described later, all these means are independent of the apparent concentration. It is noteworthy that from (2.25) the mean burst time per actual burst in \( AT \), in an average, is \( 1/\lambda_j \), equal to the mean of the apparent burst length in \( AT \) (the mean duration of a single square). Thus the burst time distribution is exponentially distributed. Take \( 1/\lambda_j \), in, of course, the mean length of time for which a square would be occupied (i.e., a single square in \( AT \)) if the channel were incapable of opening. When the channel is capable of opening, the mean length of a single square in \( AT \) is reduced to \( 1/\lambda_j + 1/\mu_j \). This might be regarded as being a result of the opening cutting short the square in \( AT \).

However, if one looks at (1.9), (3.2), the mean length of a square is still only \( 1/\lambda_j + 1/\mu_j \), rather than \( 1/\lambda_j \), even for bursts in which an opening actually takes place, and it is therefore constant for only a single occupancy followed by dissociation (i.e., the middle burst in the upper half of figure 1). This can be interpreted as an example of length biased sampling (see, for example, Gut 1962, Colquhoun).

1971, appendix 2). The longer occupancies will be more likely to have openings than the shorter occupancies. An analogous case arises with drugs that selectively block open channels (Bodian & Stühmer 1978; Colquhoun & Stühmer 1980; Colquhoun 1981).

**Distribution of the shut time**

States \( T \) and \( AT \) are shut, and, as in (F), to find the distribution of all shut periods, the methods described in (F) can be used if we redefine state \( 0 \) as the compound shut state \( (T \cdot AT) \), so that state \( 0 \) consists of AR only. The state must be reordered to bring \( T \cdot AT \) into the upper left corner of \( Q \), then

\[ \gamma_{s}^{T \cdot AT} \]

(2.29)

The partition of \( Q \) defined in (1.1) is therefore

\[ Q = \begin{bmatrix} Q_{0,0} & Q_{0,1} & Q_{0,2} & 0 \\ Q_{1,0} & Q_{1,1} & Q_{1,2} & 0 \\ Q_{2,0} & Q_{2,1} & Q_{2,2} & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix} \]

(2.29)

An analysis exactly analogous to that already given in (3.7)-(3.19) gives the Laplace transforms of the p.d.f.'s of the lifetimes in the shut state \( (T \cdot AT) \), given that the square in \( (T \cdot AT) \), and its exits (as it must) to \( AR \) as

\[ \phi_{s}(s) = \rho_{s} + \lambda_{s}(\rho_{s} + \lambda_{s}) \phi_{s}(s) + \lambda_{s}(\rho_{s} + \lambda_{s}) \phi_{s}(s); \]

(3.20)

and for the case that the square in \( (T \cdot AT) \) enters \( AR \) as

\[ \phi_{s}(s) = \rho_{s} + \lambda_{s}(\rho_{s} + \lambda_{s}) \phi_{s}(s) + \lambda_{s}(\rho_{s} + \lambda_{s}) \phi_{s}(s). \]

(3.21)

Inversion of these, by (4.60), gives the conditional p.d.f.'s as

\[ f_{s}(t) = \frac{\lambda_{s}(\rho_{s} + \lambda_{s})}{\rho_{s} + \lambda_{s}} \left( e^{-\lambda_{s} t} - e^{-\rho_{s} t} \right) \]

(3.22)

where

\[ e^{-\rho_{s} t} - e^{-\lambda_{s} t} = e^{-k t} - e^{-\phi t}. \]

(3.23)

The rate constants are solutions of the quadratic \( \phi_{s} = \rho_{s} + k \), i.e.,

\[ \lambda_{s} = \rho_{s} + k, \quad \rho_{s} = \rho_{s} + k; \]

(3.24)

The unconditional distribution of time spent in the shut state, \( f_{s}(t) \), follows from (1.38), and is simply

\[ f_{s}(t) = f_{s}(t). \]

(3.25)

because, from (1.27) and (2.28), we have \( \phi = 1 \). This is as expected because, for this theory, a shut period must last in \( AT \).
The mean short lifetime corresponding to (2.34) and (2.35) are

\[ \lambda_{m} = \lambda_{i} - \frac{1}{\lambda_{i} + \lambda_{e}} \frac{1}{\lambda_{e} + \lambda_{i}} \]

(2.37)

\[ \lambda_{m} = \lambda_{i} - \frac{1}{\lambda_{i} + \lambda_{e}} \frac{1}{\lambda_{e} + \lambda_{i}} \]

(2.38)

These mean short lifetime decreases with against concentration: they are inversely related to \( \lambda_{i} \), and these expressions are hyperbolic related to \( \lambda_{m} \). If binding is sufficiently fast, then the distribution of all short periods, \( \phi(\tau) \), approaches a simple exponential distribution with mean \( \tau_{m} = (1 + \lambda_{i})/\lambda_{m} \), which, in this case, is simply the mean of the effective channel opening rate (see, for example, Doolen & Hawkins 1972, eq. (29)).

The approximated values for \( \tau_{m} \) are obtained from (2.34) and (2.35), which are exponentially distributed, thus

\[ \phi(\tau) = \frac{1}{\lambda_{m}} e^{-\lambda_{m} \tau} \]

with mean \( \tau_{m} = 1/\lambda_{m} \).

Distribution of the apparent gap between bursts

Note that the apparent gap consists (see figure 1) of the sum of \( \tau_{i} \) a sum in AT and \( \tau_{e} \), and \( \tau_{m} \) a sum in the composite state, \( \tau_{m} \), that starts in AT and ends in AT. The p.d. of the gap, respectively, is equal to the sum of \( \lambda_{i}-\lambda_{e} \), from (2.30), the Laplace transform of which is \( \lambda_{i}^{-1} f_{p}(s) \), where \( \lambda_{i} \), in the case of the apparent gap, \( g(s) \), is shown in (2.21), its Laplace transform is

\[ \Phi(\tau) = \lambda_{i}^{-1} f_{p}(s) \]

(2.40)

The inverse transform of this, by (1.46), gives the p.d. as

\[ f_{g}(\tau) = \lambda_{i}^{-1} f_{p}(s) \]

(2.41)

The mean length of the apparent gap is most easily found as \( -1 \cdot \int \lambda_{i}^{-1} f_{p}(s) ds \), in

\[ \lambda_{m} = \lambda_{i}^{-1} f_{p}(s) \]

(2.42)

The p.d. \( f_{g}(\tau) \) given in (2.40) will be correct only if \( \lambda_{i} \), \( \lambda_{e} \), and \( \lambda_{m} \) are all different. However, \( \lambda_{i} \), \( \lambda_{e} \), \( \lambda_{m} \), and \( \lambda_{e} \) are all different.

and so \( \lambda_{i} > \lambda_{e} > \lambda_{m} \), it is likely to be due to low against concentrations (for example, in Doolen & Hawkins 1972, fig. 1), \( \lambda_{e} = 17.024 \times 10^{-4} \) and \( \lambda_{i} = 2.000 \times 10^{-4} \). In such instances, from (2.40)

\[ \Phi(\tau) = \lambda_{i}^{-1} f_{p}(s) \]

(2.43)

\[ f_{g}(\tau) = \lambda_{i}^{-1} f_{p}(s) \]

(2.44)

\[ \text{mean} \lambda_{m} = \lambda_{i}^{-1} f_{p}(s) \]

(2.45)

Probability that a short period is in a burst: use of Blyth's theorem

The distribution of all short periods, \( f_{p}(s) \), given by (2.30) and (2.31), may be expressed as a mixture of the distribution \( f_{s}(s) \) of short periods within bursts, \( f_{s}(s) = \lambda_{s}^{-1} f_{p}(s) \), and \( f_{s}(s) = \lambda_{e}^{-1} f_{p}(s) \) of short periods between bursts (i.e., apparent gap, \( f_{g}(s) \), given by (2.41)). From the rule of probability we can write

\[ f_{s}(s) = \lambda_{s}^{-1} f_{p}(s) + \lambda_{e}^{-1} f_{p}(s) \]

(2.46)

\[ \Phi(\tau) = \lambda_{i}^{-1} f_{p}(s) \]

(2.47)

\[ f_{g}(\tau) = \lambda_{i}^{-1} f_{p}(s) \]

(2.48)

\[ \text{mean} \lambda_{m} = \lambda_{i}^{-1} f_{p}(s) \]

(2.49)

\[ f_{s}(s) = \lambda_{s}^{-1} f_{p}(s) + \lambda_{e}^{-1} f_{p}(s) \]

(2.50)

A numerical illustration of this result is given later.
Stochastic properties of ion channels

The $\xi_i$ values are defined by (1.32) with the numbering convention in (3.1), i.e., they are defined by Q channels in (3.10); hence $\xi_i = \tau_i = 1$. As required for a distribution,

$$\sum_i \xi_i = 1.$$  

\[\text{(3.4)}\]

![Figure 2](image.png)

**Figure 2:** Logarithmic representation of possible behavior of single channel based on effects (3.4). Upper part shows actual likelihood of system; lower part shows counter representation of the single channel situation, and the mean number of openings per burst is

$$\bar{\xi} = \sum_i \xi_i,$$


The number of openings per burst is found by enumerating the possible modes between leaving state $T$ and returning to it, by which $\xi$ openings can be produced. Wherever state $T_A$, $\xi_T$, is entered there is the possibility of any number $0 \leq n < \xi_T$ of $\xi_T$-transitions before leaving for $T$ or for $A_T$. Therefore, from (1.32) and (1.34) the probability of being no openings is

$$P(0) = \tau_1 - \xi_T \tau_0,$$

\[\text{(3.3)}\]

and, for $\xi \geq 1$ openings,

$$P(\xi) = \xi_1 \xi_2 \xi_3 \cdots (1 - \xi_1 \xi_2 \xi_3),$$

\[\text{(3.4)}\]

where no-defect, for hysteresis,

$$\tau_T = \xi_T/(1 - \xi_1 \xi_2 \xi_3),$$

\[\text{(3.5)}\]
Distribution of the total length

The number of states shown in (3.1) will be used. We are interested in the composed state \( (T, A, T', A') \), which we shall define as \( \alpha' \). The partition of \( Q \) defined in (1.1) is therefore

\[
\begin{align*}
Q_{\alpha'} &= \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}, \\
\end{align*}
\]

or

\[
\begin{align*}
\Phi_{\alpha'} &= \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}.
\end{align*}
\]

Therefore, from (1.14),

\[
G_{\alpha'}(t) = \begin{pmatrix} 1 \exp(-\lambda T) & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix}.
\]

Then

\[
\begin{align*}
\gamma_{\alpha'}(s) &= \begin{pmatrix} 1 \exp(-\lambda T) & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix}, \\
\end{align*}
\]

or

\[
\begin{align*}
\gamma_{\alpha'}(s) &= \begin{pmatrix} 1 \exp(-\lambda T) & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix}.
\end{align*}
\]

where \( \lambda_T, \lambda_A, \lambda_{T', A'} \) are the mean eigenvalues of \( Q_{\alpha'} \), i.e., the roots of the cubic equation

\[
\lambda^3 + \beta \lambda^2 + \gamma \lambda + \delta = 0,
\]

where

\[
\begin{align*}
\beta &= -\text{tr}(Q_{\alpha'}) = \lambda_T + \lambda_A + \lambda_{T', A'} = -\beta, \\
\gamma &= \lambda_T \lambda_A + \lambda_{T'} \lambda_{A'} + \lambda_{T', A'} \lambda_T = -\gamma, \\
\delta &= \lambda_T \lambda_A \lambda_{T'} + \lambda_{T'} \lambda_{A'} \lambda_T + \lambda_T \lambda_A \lambda_{T'} = -\delta.
\end{align*}
\]

The exact solutions, and approximations to them, can be found explicitly as described, for example, by Copenhaver (1944). From (3.12) and (3.17) it follows that all \( G_{\alpha'}(t) \) (or \( \gamma_{\alpha'}(s) \), i.e., \( i = T, A, T', A' \)) are unity because state \( 4 (T) \) must be reached when \( \alpha' \) is lost. Therefore, from (1.18), the Laplace transform of the p.d.f. of the lifetimes in \( \alpha' \) are given simply by the \( G_{\alpha'}(t) \) in (3.12), as indicated in (3.13). These distributions are conditional only on the state in which the subject is in \( \alpha' \) at the start because there is only one way that the states can end.

The transform of the p.d.f. of the unconditional life in \( \alpha' \), i.e., of the burn length, is simply

\[
\mathcal{F}(s) = \gamma_{\alpha'}(s),
\]

because, from (1.27) and (3.9),

\[
\Phi = \begin{pmatrix} 0 & 0 \\ 0 & 0 \end{pmatrix}.
\]

\[
\begin{align*}
\mathcal{F}(s) &= \gamma_{\alpha'}(s), \\
\end{align*}
\]

i.e., all actual burnouts must start in state \( 4 (T) \) and end in state \( 4 (T) \).

Statistical properties of ion channels

The actual p.d.f.s can be found by inversion of (3.13), (3.14) with (1.40). For conciseness, we define

\[
\mathcal{F}_A = \frac{v}{v + \lambda_A} - \lambda_A, \\
\mathcal{F}_B = \frac{v}{v + \lambda_B} - \lambda_B, \\
\mathcal{F}_C = \frac{v}{v + \lambda_C} - \lambda_C, \\
\mathcal{F}_D = \frac{v}{v + \lambda_D} - \lambda_D, \\
\mathcal{F}_E = \frac{v}{v + \lambda_E} - \lambda_E.
\]

With these definitions, the p.d.f. of the life in \( (AT, A'T, A'T') \), given that the life starts in \( (AT) \), which is also the unconditional p.d.f. of burn length, from (3.18), is

\[
f(t) = \mathcal{F}_A(t), \quad \int_0^t \mathcal{F}_A(x) \, dx = \mathcal{F}_A(t) = \int_0^t \mathcal{F}_A(x) \, dx = \mathcal{F}_A(0) = \mathcal{F}_A(0).
\]

With mean

\[
\mu_A = \mathcal{F}_A(x) = \int_0^\infty \mathcal{F}_A(x) \, dx = \frac{1}{\lambda_A} = \frac{1}{\lambda_A},
\]

\[
\mu_B = \int_0^\infty \mathcal{F}_B(x) \, dx = \frac{1}{\lambda_B},
\]

\[
\mu_C = \int_0^\infty \mathcal{F}_C(x) \, dx = \frac{1}{\lambda_C},
\]

\[
\mu_D = \int_0^\infty \mathcal{F}_D(x) \, dx = \frac{1}{\lambda_D},
\]

\[
\mu_E = \int_0^\infty \mathcal{F}_E(x) \, dx = \frac{1}{\lambda_E}.
\]

With mean

\[
\mu_A = \frac{1}{\lambda_A}, \quad \mu_B = \frac{1}{\lambda_B}, \quad \mu_C = \frac{1}{\lambda_C}, \quad \mu_D = \frac{1}{\lambda_D}, \quad \mu_E = \frac{1}{\lambda_E}.
\]

The last result can be obtained, more simply, directly from eq. (74) of Copenhaver & Hawkins (1977), if \( \Phi' \) is substituted for \( \Phi \).

Similarly, given that the burn starts in \( (AT, A'T) \), the p.d.f. is

\[
f(t) = \mathcal{F}_2(t) = \frac{1}{\lambda_A} \int_0^t \mathcal{F}_2(x) \, dx = \frac{1}{\lambda_A} \mathcal{F}_2(t) = \frac{1}{\lambda_A} \mathcal{F}_2(0).
\]

With mean

\[
\mu_A = \frac{1}{\lambda_A}, \quad \mu_B = \frac{1}{\lambda_B}, \quad \mu_C = \frac{1}{\lambda_C}, \quad \mu_D = \frac{1}{\lambda_D}, \quad \mu_E = \frac{1}{\lambda_E}.
\]

and, given that the burn starts in \( AT \),

\[
f(t) = \mathcal{F}_3(t) = \frac{1}{\lambda_A} \int_0^t \mathcal{F}_3(x) \, dx = \frac{1}{\lambda_A} \mathcal{F}_3(t) = \frac{1}{\lambda_A} \mathcal{F}_3(0).
\]

With mean

\[
\mu_A = \frac{1}{\lambda_A}, \quad \mu_B = \frac{1}{\lambda_B}, \quad \mu_C = \frac{1}{\lambda_C}, \quad \mu_D = \frac{1}{\lambda_D}, \quad \mu_E = \frac{1}{\lambda_E}.
\]

It may be noted that \( \mu_A > \mu_B > \mu_A \) might be expected from the proximity of the starting state to state \( 4 (T) \), to which all burnouts must exit.

We now wish to find the distribution and mean of the burn length of the apparent burn, but before this can be done it is necessary to consider the distributions of time spent in \( (AT, A'T) \), because the short periods within the burn are spent in this composed state. This analysis will, for example, give the distribution of gaps within the apparent burn.

Distribution of time spent in composed gap states

We now define the composed state \( 5 (AT, A'T) \). Therefore state \( 5 \) consists of \( (T, A'B, \cdot) \). In this case there are two ways in which a subject in \( 5 \) can end (next to \( T \), or to \( A'B \)), and so the conditional distributions described in the first section must be used in their full generality for the first time. The numbering of states shown in
224 D. Colophon and A. G. Howkins

(3.4) can be used, so \( G \) is as shown in (3.10) except that it is now partitioned as follows.

\[
G = \begin{pmatrix}
0 & Q_{xy} & Q_{xt} & 0 & Q_{y} & 0 \\
0 & 0 & 2
\end{pmatrix}
\begin{pmatrix}
0 & 1 & 0 & 0 & 0 & 0 \\
0 & 0 & 2
\end{pmatrix}
\begin{pmatrix}
0 & 1 & 0 & 0 & 0 & 0 \\
0 & 0 & 2
\end{pmatrix}
\]

(3.37)

Then, from (1.14),

\[
G_{ij} = \frac{3}{4} \left( Q_{ij} + 2Q_{xi} \right) + \frac{1}{2} \left[ \omega \right]_{ij} = 0, \text{ } \quad \text{for } i \neq j
\]

(3.38)

The initial states \( (j, \lambda_{2}, \lambda_{x}) \) and \( (j, \lambda_{3}, \lambda_{x}) \) are indicated in (3.39), and \( \lambda_{2}, \lambda_{3} \) are the roots of the quadratic \( (k - \lambda_{2}, \lambda_{x}) \), in which

\[
\begin{align*}
\lambda_{2} &= \lambda_{0} + \lambda_{1} + \lambda_{2} + 2k + 2k_{1}, \\
\lambda_{3} &= \lambda_{0} + \lambda_{1} + \lambda_{2} + 2k + 2k_{1}
\end{align*}
\]

(3.39)

and

\[
\lambda_{2}, \lambda_{3} = 0, \text{ } \text{if } \lambda_{x} = 0
\]

(3.40)

From (3.30) to have

\[
G_{ij} \cdot \mu_{i} = \frac{1}{k_{2}} \lambda_{2} \left( k_{2} + k_{3} ight) + \frac{1}{k_{2}} \lambda_{3} \left( k_{2} + k_{3} ight)
\]

(3.31)

If the elements of (3.29) are divided by the ratio-adjusting elements of (3.28), we obtain, according to (1.10), the Laplace transforms of the p.d.f.s of the conditional distributions of the time spent in \( (j, \lambda_{2}, \lambda_{1}) \) in \( (j, \lambda_{3}, \lambda_{1}) \). These are as follows.

(1) The p.d.f. of the time spent in \( (j, \lambda_{2}, \lambda_{1}) \) given that the jump starts in \( (j, \lambda_{3}, \lambda_{1}) \) and exits to \( (j, \lambda_{2}, \lambda_{1}) \), turns out to be the same as the p.d.f. given that the jump starts in \( (j, \lambda_{3}, \lambda_{1}) \) and exits to \( (j, \lambda_{2}, \lambda_{1}) \). The Laplace transform being

\[
\beta_{ij} = \beta_{ij}(0) + \lambda_{j} \lambda_{i} \lambda_{i} \lambda_{j} + \lambda_{j} \lambda_{j} \lambda_{i} \lambda_{i}
\]

(3.31)

Inversion, by (1.46), gives the p.d.f. as

\[
\beta_{ij}(x) = \frac{1}{\lambda_{j} \lambda_{j} \lambda_{i} \lambda_{i}} \left( e^{x \lambda_{j} \lambda_{j} \lambda_{i} \lambda_{i}} - e^{x \lambda_{j} \lambda_{j} \lambda_{i} \lambda_{i}} \right)
\]

(3.31)

with mean lifetime

\[
\mu_{ij} = \frac{1}{\lambda_{j} \lambda_{j} \lambda_{i} \lambda_{i}} \left( 1 - e^{-x \lambda_{j} \lambda_{j} \lambda_{i} \lambda_{i}} \right)
\]

(3.31)

which cannot be expressed in terms of the chosen rate constants by (3.29) and (3.30).

(2) The p.d.f. of the time spent in \( (j, \lambda_{2}, \lambda_{1}) \), given that the jump starts in

\[
\beta_{ij}(0) = \lambda_{j} \lambda_{j} \lambda_{i} \lambda_{i}
\]

(3.32)

Notice that this corresponds to the distribution of the life in \( (j, \lambda_{2}, \lambda_{1}) \), with mean \( (\lambda_{2} + \lambda_{1})^{-1} \), from \( f_{ij} = f_{ij}(0) \) (see (3.33) and (3.34)). Inversion of (3.37) by (1.46) gives the p.d.f. as

\[
\beta_{ij}(x) = \frac{1}{\lambda_{j} \lambda_{j} \lambda_{i} \lambda_{i}} \left( e^{x \lambda_{j} \lambda_{j} \lambda_{i} \lambda_{i}} - e^{x \lambda_{j} \lambda_{j} \lambda_{i} \lambda_{i}} \right)
\]

(3.32)

The mean lifetime of the effort being is therefore

\[
\mu_{ij} = \lambda_{j} \lambda_{j} \lambda_{i} \lambda_{i}
\]

(3.33)

where \( \mu_{ij} = (\lambda_{2} + \lambda_{1})^{-1} \) is the mean life of \( (j, \lambda_{2}, \lambda_{1}) \).

(3) The last doubly conditional distribution of the effort in \( (j, \lambda_{2}, \lambda_{1}) \) is the distribution given that the jump starts in \( (j, \lambda_{2}, \lambda_{1}) \) and exits to \( (j, \lambda_{3}, \lambda_{1}) \). This is the distribution of jumps within the apparent burst (see Figure 2). Its Laplace transform is

\[
\beta_{ij}(0) = \lambda_{j} \lambda_{j} \lambda_{i} \lambda_{i}
\]

(3.33)

i.e., the distribution of the life in \( (j, \lambda_{2}, \lambda_{1}) \). Inversion by (1.46) gives

\[
\beta_{ij}(x) = \lambda_{j} \lambda_{j} \lambda_{i} \lambda_{i} \left( e^{x \lambda_{j} \lambda_{j} \lambda_{i} \lambda_{i}} - e^{x \lambda_{j} \lambda_{j} \lambda_{i} \lambda_{i}} \right)
\]

(3.34)

with mean \( (\lambda_{2} + \lambda_{1})^{-1} \) jumps within the apparent burst

\[
\mu_{ij} = \lambda_{j} \lambda_{j} \lambda_{i} \lambda_{i}
\]

(3.35)

The distributions of the life in \( (j, \lambda_{2}, \lambda_{1}) \) conditioned only on the starting state can be found, from (1.14). Their Laplace transforms are the row sums of (3.39), and inversion gives their p.d.f. as follows.

(4) The p.d.f. of the life in \( (j, \lambda_{2}, \lambda_{1}) \), i.e., in \( (j, \lambda_{2}, \lambda_{1}) \), given that the jump starts in \( (j, \lambda_{2}, \lambda_{1}) \), but regardless of what state follows, is

\[
\beta_{ij}(x) = \lambda_{j} \lambda_{j} \lambda_{i} \lambda_{i} \left( e^{x \lambda_{j} \lambda_{j} \lambda_{i} \lambda_{i}} - e^{x \lambda_{j} \lambda_{j} \lambda_{i} \lambda_{i}} \right)
\]

(3.36)

with mean

\[
\mu_{ij} = \lambda_{j} \lambda_{j} \lambda_{i} \lambda_{i}
\]

(3.37)

The p.d.f. of the time spent in \( (j, \lambda_{2}, \lambda_{1}) \), given that the jump starts in

\[
\beta_{ij}(0) = \lambda_{j} \lambda_{j} \lambda_{i} \lambda_{i}
\]

(3.38)

The distribution cannot be expressed in terms of the chosen rate constants by (3.29) and (3.30).

(5) The p.d.f. of the time spent in \( (j, \lambda_{2}, \lambda_{1}) \), given that the jump starts in \( (j, \lambda_{2}, \lambda_{1}) \), but regardless of what state follows, is

\[
\beta_{ij}(x) = \lambda_{j} \lambda_{j} \lambda_{i} \lambda_{i} \left( e^{x \lambda_{j} \lambda_{j} \lambda_{i} \lambda_{i}} - e^{x \lambda_{j} \lambda_{j} \lambda_{i} \lambda_{i}} \right)
\]

(3.39)

with mean

\[
\mu_{ij} = \lambda_{j} \lambda_{j} \lambda_{i} \lambda_{i}
\]

(3.40)
Finally, the unconditional distribution of the lifetime of a specimen in \((AT, AT')\) follows from (2.29). From (2.32) and (2.27),

\[
P_{i}(x|\alpha, \beta) = \frac{\alpha^{x} \beta^{\alpha-x}}{\Gamma(\alpha)}
\]

so

\[
\Phi \equiv \Phi(\alpha, \beta) = \frac{\alpha^{x} \beta^{\alpha-x}}{\Gamma(\alpha)}
\]

(3.4.1)

Therefore, from (3.38), (3.32) and (3.33), the unconditional p.d.f. of the life is of the form

\[
\Phi_{i}(t|\lambda_{1}, \lambda_{2}, \beta) = \frac{\beta^{\lambda_{1}t} \lambda_{2}^{\lambda_{1}t}}{\Gamma(\lambda_{1})} e^{-\lambda_{2}t}
\]

(3.4.2)

another weighted sum of the same two exponential terms. The mean of this distribution is

\[
\mu_{r} = (1 + \lambda_{1} + \lambda_{2}) + \beta
\]

(3.4.3)

This mean can also be found, more easily, from the appropriate analogies of Udupchaphani & Hawkins (1975, eq. 74). This mean life is \((AT, AT')\) will decrease with increase in ageing concentration if \(\lambda_{1} > \beta\), and increase with increase in ageing concentration if \(\lambda_{1} < \beta\).

Note that the time spent in \((AT, AT')\), \(\alpha_{i}\), given that the specimen starts in \(AT\) and exits \(T\), has a p.d.f. given by (3.38) and (3.32), denoted \(f_{\alpha_{i}}(t)\). Furthermore, this interval consists of two parts: (a) an apparent burst (with \(P(\alpha_{i}|t)\) and \(\mu_{n}\)), (b) or (b) a period in \((AT, AT')\) that is, so that its p.d.f. is \(f_{\mu_{n}}(t)\), which is specified in (3.32). Therefore, from (3.32),

\[
f_{\alpha_{i}}(t) = f_{\mu_{n}}(t) P(\alpha_{i}|t)
\]

(3.4.4)

i.e., from (3.1.2), (3.13), (3.1.17) and (3.1.4),

\[
f_{\alpha_{i}}(t) = \int f_{\mu_{n}}(t) P(\alpha_{i}|t) dt
\]

(3.4.5)

Inversion of this by \(\mu_{n}\) gives the p.d.f. in the form of sums of exponentials with the same rate constants as for the actual burst, namely

\[
\mu_{n} = \lambda_{1} t + \lambda_{2} t - (\lambda_{1} + \lambda_{2}) t
\]

(3.4.6)

The mean length of the apparent burst is therefore

\[
\mu_{n} = \lambda_{1} t + \lambda_{2} t - (\lambda_{1} + \lambda_{2}) t
\]

(3.3.3)

which is, as not surprisingly, \(\mu_{n}\) given by (3.38) times \(\mu_{n}\) given by (3.36). It must increase with ageing concentration.
The Laplace transforms of the p.d.f. of the unconditional lifetime of the shot state is
\[ f(t) = \mathcal{L} \{ f(t) \}. \]

The right side of (4.68) is the sum of a Dirac delta function and a Gamma distribution. The mean of this distribution is given by (4.70) as
\[ \mu = \frac{k}{\alpha}. \]

The parameter \( k \) is given by (4.71) as
\[ k = \frac{\alpha}{\beta}. \]

The variance of the Gamma distribution is given by (4.72) as
\[ \text{Var} = \frac{\beta^2}{\alpha^2}. \]

The skewness of the Gamma distribution is given by (4.73) as
\[ \text{Skew} = 2 \frac{\beta}{\alpha}. \]

The excess kurtosis of the Gamma distribution is given by (4.74) as
\[ \text{Kurtosis} = 6 \frac{\beta^2}{\alpha^2}. \]

The coefficients of skewness of the Gamma distribution are given by (4.75) as
\[ \text{Kurtosis} = 6 \frac{\beta^2}{\alpha^2}. \]

The Pearson's product-moment correlation coefficient of the Gamma distribution is given by (4.76) as
\[ \rho = \frac{\beta}{\alpha}. \]

The coefficient of skewness of the Gamma distribution is given by (4.77) as
\[ \text{Skew} = 2 \frac{\beta}{\alpha}. \]

The median of the Gamma distribution is given by (4.78) as
\[ \text{Median} = \frac{\alpha}{2}. \]

The mean of the Gamma distribution is given by (4.79) as
\[ \mu = \frac{\alpha}{2}. \]

The variance of the Gamma distribution is given by (4.80) as
\[ \text{Var} = \frac{\alpha^2}{4}. \]

The skewness of the Gamma distribution is given by (4.81) as
\[ \text{Skew} = 2 \frac{\alpha}{2}. \]

The excess kurtosis of the Gamma distribution is given by (4.82) as
\[ \text{Kurtosis} = 6 \frac{\alpha^2}{4}. \]

The coefficient of skewness of the Gamma distribution is given by (4.83) as
\[ \text{Skew} = 2 \frac{\alpha}{2}. \]

The median of the Gamma distribution is given by (4.84) as
\[ \text{Median} = \frac{\alpha}{2}. \]

The mean of the Gamma distribution is given by (4.85) as
\[ \mu = \frac{\alpha}{2}. \]

The variance of the Gamma distribution is given by (4.86) as
\[ \text{Var} = \frac{\alpha^2}{4}. \]

The skewness of the Gamma distribution is given by (4.87) as
\[ \text{Skew} = 2 \frac{\alpha}{2}. \]

The excess kurtosis of the Gamma distribution is given by (4.88) as
\[ \text{Kurtosis} = 6 \frac{\alpha^2}{4}. \]

The coefficient of skewness of the Gamma distribution is given by (4.89) as
\[ \text{Skew} = 2 \frac{\alpha}{2}. \]

The median of the Gamma distribution is given by (4.90) as
\[ \text{Median} = \frac{\alpha}{2}. \]

The mean of the Gamma distribution is given by (4.91) as
\[ \mu = \frac{\alpha}{2}. \]

The variance of the Gamma distribution is given by (4.92) as
\[ \text{Var} = \frac{\alpha^2}{4}. \]

The skewness of the Gamma distribution is given by (4.93) as
\[ \text{Skew} = 2 \frac{\alpha}{2}. \]

The excess kurtosis of the Gamma distribution is given by (4.94) as
\[ \text{Kurtosis} = 6 \frac{\alpha^2}{4}. \]

The coefficient of skewness of the Gamma distribution is given by (4.95) as
\[ \text{Skew} = 2 \frac{\alpha}{2}. \]

The median of the Gamma distribution is given by (4.96) as
\[ \text{Median} = \frac{\alpha}{2}. \]

The mean of the Gamma distribution is given by (4.97) as
\[ \mu = \frac{\alpha}{2}. \]
with rate constants \( k_1, k_2, \ldots, k_n \) as long as these are all different from each other.

The mean length of the apparent gap, found as \(-\frac{1}{2} \ln(2) \langle g \rangle \), is

\[
\langle g \rangle = k_1^{-1} + k_2^{-1} + \cdots + k_n^{-1}.
\]

In particular cases, however, some of the \( k_i \) may be very similar. For example, if \( k_1 \approx k_2 \approx k_3 \), and the apparent concentration is not too high, it follows from (1.6) to (1.23) and (2.45) to (2.85), that \( k_i \approx k_2 \approx k_3 \), and, perhaps, \( k_2 \approx k_3 \approx k_4 \).

This can be inverted by (1.2) to give a p.d.f. that involves only three exponential terms, which may be in turn, to

\[
\text{Probability that a shot period is part of a burst: use Boyes' theorem.}
\]

The distributions of all shot periods, \( f_{\text{all}} \), given by (1.7), may be expressed as a sum of shot periods within bursts, \( f_{\text{in burst}} \), given by (2.41), and (b) of shot periods between bursts (i.e. of apparent gaps, \( f_{\text{gap}} \)), given by the inverse of (1.7). To apply (2.4) we require

\[
P = \text{probability of a shot;}
\]

\[
P(\text{in AT, } A, \text{ shot rates to } A, \text{ shot rates in AT})
\]

from (1.17) to (1.31). Thus, from (2.43), the required combination of distributions is

\[
f_{\text{all}} = f_{\text{in burst}} + f_{\text{gap}} (1 - P_{\text{in burst}}).
\]

Boyes' theorem can now be applied, as in (2.49) and (2.56), to obtain the probability distribution of a shot period of length \( t \) in a shot period within a burst as

\[
P(\text{shot period in burst; length } = t) = \frac{1}{1 - P_{\text{in burst}}} f_{\text{in burst}} ( \text{at } t).
\]

A numerical illustration of this result is given later.

Numerical examples

The foregoing results will now be illustrated by means of some numerical calculations. We shall suppose (a) an average shot length of 1 mm, and so on = 1000 nm; (b) a rather effective anchor, capable of opening 90% of the time; and (c) a diffusion rate constant of 100 nm/sec, which, although fast compared with a, is not fast enough for the extreme fast binding case to be approached closely.

This diffusion rate would, for example, imply a diffusion rate constant of 2.3 \times 10^{-6} cm/sec for an anchor with an effective constant for binding of 10 nm/sec. (Does et al. 1971; Sleserian & Loret 1977; Salamon & Adams 1977) this is always appropriate for the diffusion limit for an association rate constant. We shall also choose, in both of the examples below, an anchor concentration that occurs 4.5 times, that is, 0.51 times, to open at equilibrium, although this would not produce a large response.
of the apparent gap can be written \( f_{gap} = \frac{15}{4} f \) (see (28, 29)). From (2.34), with mean \( \mu_{gap} = 38.8 \times 10^{-6} \). After a short time this is close to a simple exponential distribution with mean 38.7 ms.

The probability that a short period of time \( T \) is within a burst (mean length 23.4 ms, rather than an apparent gap (mean length 38.4 ms), is given by (2.36). It decreases quite rapidly in the range of from 300 to 4000 ms, and is 0.35 for \( T = 1750 \) and 0.05 for \( T = 2000 \) ms. Thus a short period of length 1750 ms has a 19 to 1 chance of being a gap within a burst, and a short period of 300 ms has a 19 to 1 chance of being a gap between bursts.

Cognitive mechanisms

The parameters and will be as above, and independent binding areas will be assumed, as \( E = \sqrt{\frac{g}{k}} = 10^{10} \). To have \( a = 4.7 \) of channels open, a higher agonist concentration \( H = 2.4 \times 10^{-11} \) would correspond to \( \alpha = 1.45 \times 10^{-4} \) for an agonist with an equilibrium binding constant of 38.9 ms.

Numerical calculations by the methods described in Coburn and Hawkins (1977) show that in the case the predicted noise spectrum is a close approximation to a Lorentzian with center constant \( \lambda = 32.5 \times 10^{-3} \), so the apparent open lifetime is \( a = 2.3 \times 10^{-3} \). This is somewhat non-receptor mechanism but still quite short as long as the true apparent lifetime is 1 ms. The moment and fast components in the moment-fast model would have \( \mu > 0 \), \( \sigma > 0 \), \( \alpha > 0 \) and \( \beta > 0 \) in close accordance with the mean, which is a simple explanation for small that they would not be detectable. The exponentially distributed lifetime for which the individual areas have \( \mu = 29.5 \), \( \sigma = 29.5 \), \( \alpha = 29.5 \), \( \beta = 29.5 \), and \( \gamma = 29.5 \) is the best value that shows that occupations are much more frequent in the cognitive mechanism, as might be expected in view of the higher agonist concentration. However, from (6.1), \( 5.46 \times 10^{-4} \) of occupied-the-bar complex. In fact, \( 9.6 \times 10^{-4} \) of all bursts consist of a single to a 0.001 transition takes place before a second ligand is bound. A further 0.23, of bursts become slowly liganded at least once, but do not open, and \( 5 \times 10^{-3} \) are 2.4 ms, have one or more openings. Thus, although the mean number of occupancy is 0.01 ms, only 0.01 are, the mean number of openings per burst, from (2.34) and (2.46). When one ligand is bound, a first channel (15) is much more likely to dissociate \( (p_{out} = 0.85) \) than to bind a second ligand (17) \( (p_{out} = 0.10) \), but once one occupied ligand is bound (15), opening \( (p_{out} = 0.85) \) is almost certain \( (p_{out} = 0.95) \). This means that channels that are already occupied may continue to open even after the agonist saturation has failed to rise (e.g. during a miniature endplate current).

The distribution of burst length

The distributions of times spent in \( \Delta T \) \( \Delta \lambda \), \( \Delta h \) \( \Delta l \) are characterized by exponentials with rate constants, from (2.14) \( \lambda = 38.7 \times 10^{-6} \). From (2.34) and (2.40), \( \lambda = 2.3 \times 10^{-6} \) and mean \( \mu_{gap} = 38.8 \times 10^{-6} \). Thus the unconditional life of the burst length has the distribution, from (2.11)

\[
\lambda_{\Delta T} = \lambda_{\Delta \lambda} = \lambda_{\Delta h} = \lambda_{\Delta l} = \lambda = 2.3 \times 10^{-6} \text{ s}^{-1}
\]